

Solvation Free Energies Calculated Using the GB/SA Model: Sensitivity of Results on Charge Sets, Protocols, and Force Fields

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ABSTRACT: The sensitivity of aqueous solvation free energies (SFEs), estimated using the GB/SA continuum solvent model, on charge sets, protocols, and force fields, was studied. Simple energy calculations using the GB/SA solvent model were performed on 11 monofunctional organic compounds. Results indicate that calculated SFEs are strongly dependent on the charge sets. Charges derived from electrostatic potential fitting to high level *ab initio* wave functions using the CHELPG procedure and "class IV" charges from AM1/CM1a or PM3/CM1p calculations yielded better results than the corresponding Mulliken charges. Calculated SFEs were similar to MC/FEP energies obtained in the presence of explicit TIP4P water. Further improvements were obtained by using GVB/6-31G** and MP2/6-31 + G** (CHELPG) charge sets that included correlation effects. SFEs calculated using charge sets assigned by the OPLSA* force field gave the best results of all standard force fields (MM2*, MM3*, MMFF, AMBER*, and OPLSA*) implemented in MacroModel. Comparison of *relative* and *absolute* SFEs computed using either the GB/SA continuum model or MC/FEP calculations in the presence of explicit TIP4P water showed that, in general, *relative* SFEs can be estimated with greater accuracy. A second set of 20 mono- and difunctional molecules was also studied and *relative* SFEs estimated using energy minimization and thermodynamic cycle perturbation (TCP) protocols. SFEs calculated from TCP calculations using the GB/SA model were sensitive to bond lengths of dummy bonds (i.e., bonds involving dummy atoms). In such cases, keeping the bond lengths of dummy bonds close to the

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corresponding bond lengths of the starting structures improved the agreement of TCP-calculated SFEs with energy minimization results. Overall, these results indicate that GB/SA solvation free energy estimates from simple energy minimization calculations are of similar accuracy and value to those obtained using more elaborate TCP protocols. © 1998 John Wiley & Sons, Inc. J Comput Chem 19: 769–780, 1998

Keywords: Solvation free energies; GB/SA solvent model; energy minimization calculations; AMBER force field; macromodel; thermodynamic cycle perturbation (TCP) calculations

Introduction

Solvation free energies for small organic molecules are important in drug design and in understanding the relationship of solvation to other molecular properties.^{1,2} Both implicit (continuum) and explicit solvent models have been employed in the past for the treatment of solvation free energies.^{3–15} Earlier Monte Carlo–free energy perturbation (MC/FEP) calculations,^{7–9} using the TIP3P and TIP4P water models in conjunction with the OPLS force field,²⁵ led to accurate predictions of solvation free energies (SFEs) of small organic molecules. That approach, however, used the thermodynamic cycle perturbation (TCP) method,²⁶ which is computationally intensive due to the need to represent explicitly hundreds of water molecules in each simulation. Hence, there is an obvious need to evaluate computationally less demanding methods for predicting SFEs accurately. The GB/SA continuum model,⁵ is particularly attractive in this respect, because it is a broadly applicable continuum model that can be used in conjunction with force fields such as AMBER,^{16,17} MM2,¹⁸ MM3,¹⁹ MMFF,^{20–24} and OPLSA²⁵ for energy calculations on organic and biological molecules in water or chloroform.

Clearly, the accurate determination of the electrostatic contribution to solvation is very important for accurate prediction of SFEs, particularly for polar solutes in polar solvents. This, in turn, is a function of the force field employed and the method of partial charge assignment. Iterative fluid simulations have also been used to develop charge models for the OPLS force field²⁵ and shown to be successful in reproducing structural and thermodynamic properties of small organic molecules. Later, a more direct charge determination procedure, such as fitting partial charges to the electrostatic potential surface of *ab initio* HF/6-31G*

wave functions, was explored and found useful.⁷ While the use of electrostatic-potential-derived charges from high-level *ab initio* calculations is also consistent with the AMBER force field,^{16,17} the MM2¹⁸ and MM3¹⁹ force fields employ experimental bond moments to parametrize electrostatic contributions. Partial charges assigned by the MMFF force field^{20–24} have been derived from high-level *ab initio* calculations, and the specific MMFF charge assignments coupled to conformational energies (and torsional parameters) fitted to a large number of molecules. Hence, the user is not expected to alter these specific assignments for molecules of interest. Because charge assignments by various methods can vary considerably, it is obviously important to investigate the sensitivity of computed SFEs on different charge sets for any charge-dependent continuum solvation model. Here, an evaluation of the sensitivity of GB/SA-calculated SFEs is presented, using different charge sets, protocols, and force fields for a set of small organic molecules with experimentally known SFEs.

Methods

MOLECULAR DATABASE AND COMPUTATIONAL METHODOLOGY

SFEs were calculated for two sets of small organic molecules using the GB/SA model,⁵ available in the MacroModel package.²⁷ The first set consisted of 11 monofunctional organic molecules: methanol, methyl amide, methyl cyanide, dimethyl ether, methyl sulfide, methyl chloride, acetamide, acetic acid, acetone, methyl acetate, and pyridine. These were used for assessing the sensitivity of calculated *absolute* and relative solvation free energies (SFEs) to various charge sets derived by different procedures. The second set consisted of 20 mono- and difunctional organic molecules: acetaldehyde, ethanol, ethane, methanol, acetic acid,

methyl acetate, acetone, cyclopentane, pyrrolidine, benzaldehyde, benzene, pyridine, cyclohexane, piperidine, aniline, *meta*-hydroxybenzaldehyde, phenol, *para*-hydroxybenzaldehyde, thiophenol, 1,1,2-trichloro ethane, and 1,1,1-trichloro ethane. These were used for assessing the sensitivity of *relative* solvation free energies (Δ SFEs) computed using two different protocols and force fields.

The charge sets used for the first set of molecules were obtained from either: (a) earlier⁷ HF/6-31G* calculations; (b) semiempirical MO methods, AMI²⁸ and PM3;²⁹ (c) high-level *ab initio* quantum mechanical calculations using Gaussian-92³⁰ and PS-GVB^{31,31} programs; or (d) MacroModel²⁷ implementations of the MM2,¹⁸ MM3,¹⁹ MMFF,^{20–24} AMBER,^{16,17} and OPLSA²⁵ force fields. Geometries for these molecules were taken from *ab initio* quantum mechanical calculations reported by Carlson et al.⁷ All simulations and energy calculations reported here were performed without any cutoffs for electrostatic and van der Waals interactions. The solvation energy part of the total energy calculated for each molecule is considered to be its SFE.⁵

Molecules in the second set were geometry optimized at the HF/6-31G* basis set level using Gaussian-92.³⁰ Δ SFEs were calculated using either a protocol based on energy minimization or a protocol based on TCP. Atomic partial charges were derived by electrostatic potential fitting of the *ab initio* wave functions using the CHELPG³³ procedure and using the GVB/6-31G** method.³² Both protocols used the AMBER*–GB/SA³⁴ and OPLSA*–GB/SA force fields and charge sets from HF/6-31G* (CHELPG) calculations (used in conjunction with AMBER* and OPLSA* force fields) and GVB/6-31G** calculations (used in conjunction with the OPLSA* force field). For the first protocol, Δ SFEs were calculated for all related pairs of molecules from the corresponding SFEs (solvation components) following optimizations in GB/SA water. For the second protocol, TCP calculations²⁶ were performed using the MacroModel 5.5²⁷ program for obtaining *relative* solvation free energies for related pairs of molecules.

Figure 1 shows the thermodynamic cycle employed for estimating *relative* differences in SFEs ($\Delta\Delta G_{\text{aq}}$) of two solutes, S1 and S2. The *relative* solvation free energy difference between the two solutes may be expressed by the following equation:

$$\Delta G_2 - \Delta G_1 = \Delta G_{\text{solv}} - \Delta G_{\text{gas}} = \Delta\Delta G_{\text{aq}} \quad (1)$$

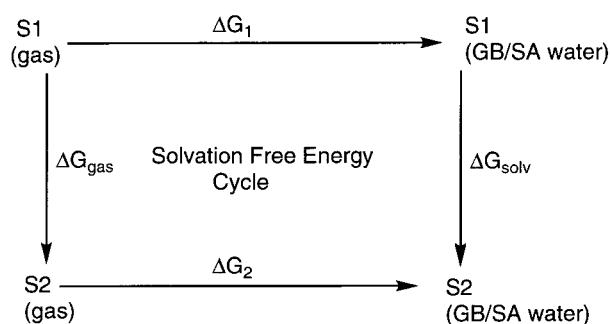


FIGURE 1. The free energy cycle used in TCP calculations for computing relative solvation free energy differences.

The free energy change for converting S1 into S2 was computed by perturbing the Hamiltonian of reactant (initial) state S1 into that of the product (final) state S2. This transformation was accomplished through a parameterization of terms comprising the interaction potentials of the system with a change of state variable that maps onto reactant and product states when that variable is 0 and 1, respectively. The total free energy change for the mutation from the initial to the final state was computed by summing “incremental” free energy changes over all the windows as the state variable changed from 0 to 1. Details of the simulation methodology as implemented in MacroModel²⁷ (versions 4.5 or higher) have been described earlier.³⁵ Initially, the starting molecule in each pair (mutation) was optimized using 1000 steps of the PRCG procedure, available in MacroModel.²⁷ The system was then equilibrated by performing a stochastic dynamics simulation for 20 ps at 298 K, with a time step of 1 fs. The same time step (1 fs) was used for all simulations (equilibration and sampling). Each mutation was accomplished over 41 windows (20 ps of equilibration and 100 ps of sampling for each window at 298 K). Thus, a total simulation time of 5 ns was used for each mutation. Data collection for each complete mutation included both forward (λ from 0 to 1) and reverse (λ from 1 to 0) simulations. The results reported in Table VI are an average of both forward and backward results. For all these *relative* solvation free energy calculations the error bars are estimated for each window by dividing the window statistics into five groups and computing the standard deviation.³⁶ The root mean square of these window errors reported in Table VI is a measure of the statistical uncertainty of results for each complete mutation and ranged from ± 0.03 to

0.65 kcal/mol. In cases where at least one rotatable bond (between heavy atoms) was present, MC/SD (combined Monte Carlo–stochastic dynamics) simulations³⁷ were performed to improve the sampling efficiency and convergence.

METHOD OF ASSESSMENT FOR SOLVATION MODELS

To assess the sensitivity of the calculated SFEs, the Pearson correlation coefficient (*R*), RMS residual (RMS), average unsigned error (AUE, obtained by taking the mean of absolute errors for each prediction corresponding to a given model), and maximum and minimum errors (max E and min E) in the predicted values were used. Predictive *r*² is a measure of the predictive capability and validity of a correlation model.³⁸ Conventional *r*² is calculated from the uncertainty after the least-squares fit has been performed. However, predictive *r*² is calculated from the uncertainty in prediction over all the compounds (press) in a data set. Therefore, predictive *r*² is always worse than traditional *r*². A value of 0.3 for predictive *r*² corresponds to the 95% confidence limit.^{39, 40}

Predictive *r*² = (SD – “press”)/SD (2)

where SD is the sum of squared deviations of each experimental SFE value from their mean and “press” is the predictive sum of squares (the sum

of squared differences between the actual and predicted SFE values). Negative values for predictive *r*² indicate that SFE is better estimated by the “mean of values” rather than by the model under consideration.

Results and Discussion

SOLVATION FREE ENERGIES FROM ENERGY CALCULATIONS USING GB/SA MODEL

SFEs were obtained from single point energy calculations using “standard” geometries reported by Carlson et al.⁷ and 13 different charge sets. Results are compared with those of Carlson et al.⁷ using MC/FEP calculations in explicit solvent.

Results Using Charge Sets Reported by Carlson et al.⁷

A comparison of the GB/SA results using the HF/6-31G* Mulliken charge sets with those using corresponding CHELPG charge sets shows that CHELPG charge sets are better with respect to all statistics: correlation coefficient, *R* = 0.57 for Mulliken vs. 0.89 for CHELPG; average unsigned error, AUE = 4.21 for Mulliken vs. 1.62 for CHELPG; root mean square residual, RMS = 2.24 for Mulliken vs. 1.22 for CHELPG; and predictive *r*² = 0.30 for Mulliken vs. 0.73 for CHELPG (Table Ia). The

TABLE I. Sensitivity of Calculated SFEs (Using the GB / SA Model) on Four Groups of Charge Sets for a Set of 11 Small Organic Molecules.^a

Group	Charge set	<i>R</i>	RMS	AUE	Min E	Max E	Pred <i>r</i> ²
(a)	HF / 6-31G* (CHELPG)	0.89	1.22	1.62	0.00	2.72	0.73
	HF / 6-31G* (Mulliken)	0.57	2.24	4.21	0.75	10.64	0.30
(b)	AM1 (Mulliken)	0.79	1.67	2.52	0.16	4.84	0.58
	PM3 (Mulliken)	0.84	1.47	2.50	1.95	5.45	0.51
	AM1 (CM1a)	0.94	0.90	0.88	0.16	1.26	0.86
	PM3 (CM1p)	0.89	1.26	1.16	0.01	3.05	0.81
(c)	MP2 / 6-31 + G** (CHELPG)	0.92	1.08	1.21	0.23	2.25	0.80
	GVB / 6-31G**	0.94	0.92	0.72	0.01	1.53	0.89
	MM2*	0.72	1.88	2.65	0.04	4.70	0.67
(d)	MM3*	0.74	1.82	1.82	0.35	4.08	0.68
	MMFF	0.83	1.51	1.97	0.38	4.79	0.67
	AMBER*	0.80	1.63	1.38	0.32	2.47	0.77
	OPLSA*	0.90	1.06	1.02	0.17	1.84	0.83
MC / FEP (OPLS) results		0.97	0.64	1.07	0.20	3.70	0.64

^a Correlation coefficient (*R*), RMS residual (RMS), average unsigned error (AUE), minimum error (Min E), and maximum error (Max E) are shown for each combination of protocol, charge set, and force field. The last column shows predictive *r*² calculated according to Eq. (2). The last line shows a summary of the results of Carlson et al.⁷

use of Mulliken charges resulted in a considerable overestimation of the magnitude of the SFEs in several cases. This observation is consistent with MC/FEP results obtained by Carlson et al.⁷ using the explicit TIP4P water model, and shows that Mulliken charge sets are not appropriate for calculating SFEs using implicit or explicit charge-dependent solvation models. When HF/6-31G* (CHELPG) charge sets were used, the MC/FEP data gave better conventional statistics: $R = 0.97$, $RMS = 0.64$, and $AUE = 1.07$, whereas with respect to predictive r^2 , the GB/SA result is clearly better:

$r^2 = 0.64$ for MC/FEP vs. 0.73 for GB/SA. Interestingly, for both MC/FEP and GB/SA data, the maximum error (max E) occurs in the case of acetamide (max E = 3.7 kcal/mol for MC/FEP vs. 2.7 for GB/SA). Figure 2a shows the scatter of experimental SFEs and GB/SA-calculated values corresponding to HF/6-31G* (CHELPG) charge sets.

Absolute SFEs using MC/FEP calculations were obtained indirectly; that is, from *relative* free energy calculations of each molecule with respect to certain key solutes. The *absolute* SFEs of these key

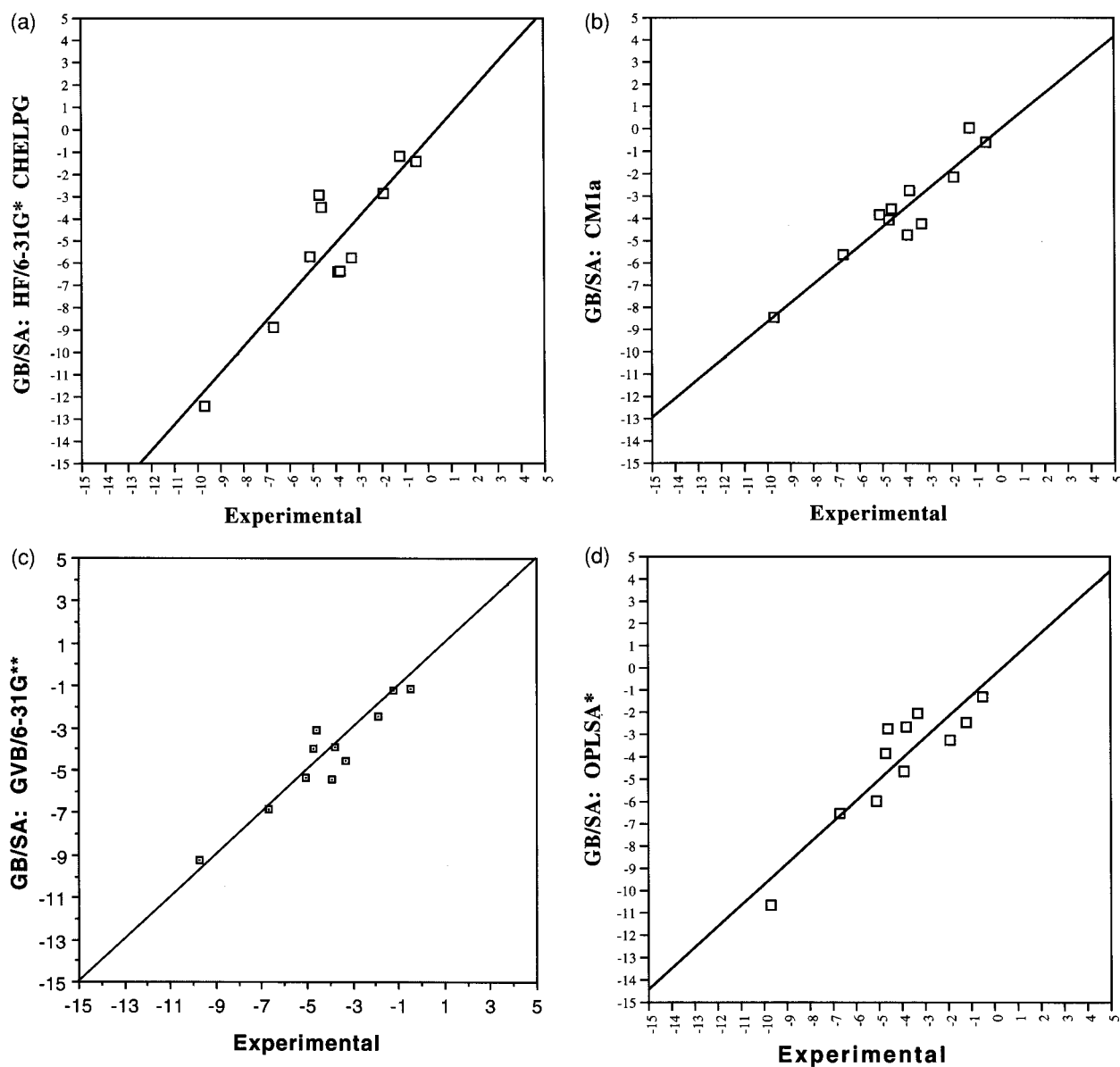


FIGURE 2. Plots of GB / SA calculated vs. experimental *absolute* solvation free energies for 11 test molecules with: (a) HF-631G* (CHELPG) charges; (b) AM1 / CM1a charges; (c) GVB / 6-31G** charges; and (d) OPLSA* charges.

solutes were obtained by shrinking the solutes to “nothing” in water through MC/FEP simulation.⁷ Because certain systematic errors tend to cancel out when computing relative free energy differences, better agreement with experimental results was expected for *relative* SFEs computed using explicit or implicit solvation models. Table III from Carlson et al.⁷ contains the data pertinent to *relative* SFEs used in the derivation of *absolute* SFEs. Using the *relative* SFE data, we obtained $R = 0.98$, $RMS = 0.70$, $AUE = 0.81$, and $\text{pred } r^2 = 0.89$, whereas the corresponding GB/SA statistics were $R = 0.96$, $RMS = 1.05$, $AUE = 0.78$, and $\text{pred } r^2 = 0.91$. Thus, *all* statistics improved for both implicit and explicit models, when *relative* SFE values were considered rather than absolute values. Statistical results using relative SFE data are listed in Table IIa.

Performance of Charge Sets Derived from Semiempirical MO Methods

Four charge sets were obtained from the semiempirical methods AM1²⁸ and PM3²⁹ using both Mulliken population analysis and class IV charges⁴¹ (CM1a and CM1p) as implemented in the AMSOL package.⁴² Summaries of the GB/SA results using these charge sets are given in Table Ib for *absolute* SFEs and in Table IIb for *relative* SFEs.

In general, the GB/SA SFEs calculated using Mulliken charges from the semiempirical MO methods (AM1 or PM3) gave somewhat better results than did the HF/6-31G* Mulliken charges. While Mulliken charges from the HF/6-31G* wave function underestimated the SFEs, those from AM1 and PM3 systematically overestimated the SFEs. However, when AM1/CM1a “class IV” charges were used, better statistics were obtained. Similarly, PM3/CM1p (“class IV”) charge sets gave better results than did the corresponding Mulliken charges. Of all the semiempirical MO methods of charge determination, AM1/CM1a charge sets gave the best results. Comparing the statistical results shown in Table Ib with those of Table IIb, it is seen that AM1 and PM3 statistics did not improve when *relative* SFEs were used, with either Mulliken charge sets or “class IV” charge sets. Figure 2b shows the scatter of experimental SFEs and calculated values corresponding to AM1/CM1a charge sets that gave the best results among the semiempirical charge sets.

Results Obtained for Charge Sets Derived from High Level Ab Initio MO Theory

Two, correlation methods were used for deriving the high level *ab initio* charge sets employed in the calculations: (i) *ab initio* (Gaussian-92) calculations at the MP2/6-31 + G** basis set level, with

TABLE II. Sensitivity of Calculated Relative SFEs (Using the GB / SA Model) on Four Groups of Charge Sets for a Set of 11 Small Organic Molecules.^a

Group	Charge set	R	RMS	AUE	Min E	Max E	Pred r^2
(a)	HF / 6-31G* (CHELPG)	0.96	1.05	0.78	0.29	1.92	0.91
	HF / 6-31G* (Mulliken)	0.70	2.54	3.46	0.03	6.50	-0.64
(b)	AM1 (Mulliken)	0.73	2.37	1.97	0.97	4.15	0.29
	PM3 (Mulliken)	0.74	1.47	2.25	0.38	4.58	0.31
	AM1 (CM1a)	0.94	1.23	1.81	0.00	2.10	0.81
	PM3 (CM1p)	0.88	1.69	1.22	0.03	2.80	0.74
(c)	MP2 / 6-31 + G**						
	(CHELPG)	0.96	0.93	0.65	0.04	1.96	0.92
	GVB / 6-31G**	0.96	0.99	0.70	0.00	1.80	0.92
(d)	MM2*	0.61	2.81	3.63	0.32	5.44	0.07
	MM3*	0.84	1.92	2.19	0.43	4.50	0.48
	MMFF	0.87	1.77	1.64	0.00	4.41	0.67
	AMBER*	0.88	1.67	2.00	0.18	3.67	0.54
	OPLSA*	0.95	1.06	0.85	0.12	2.73	0.88
MC / FEP (OPLS) results		0.98	0.70	0.81	0.00	2.00	0.89

^a Correlation coefficient (R), RMS residual (RMS), average unsigned error (AUE), minimum error (Min E), and maximum error (Max E) are shown for each combination of protocol, charge set, and force field. The last column shows predictive r^2 calculated according to Eq. (2). The last line shows a summary of the results of Carlson et al.

CHELPG³³ fitting; and (ii) *ab initio* (PS-GVB) calculations^{31,32} at the GVB/6-31G** basis set level. In the GVB/6-31G** calculations, only bonds involving heteroatoms were correlated. Statistical summaries of the GB/SA results using these two charge sets are given in Tables Ic and IIc for *absolute* and *relative* SFEs. SFEs calculated using either MP2/6-31 + G** (CHELPG) or GVB/6-31G** charges gave better statistics than the SFEs calculated using HF/6-31G* (CHELPG) charges. It appears that inclusion of electron correlation effects improves results considerably over the uncorrelated Hartree–Fock results (see Table Ia).

Among all MO methods (semiempirical or *ab initio*) the GVB/6-31G** charge sets gave the best results (for *absolute* SFEs) of all MO methods in terms of R , AUE, and pred r^2 , whereas charge sets from the semiempirical AM1/CM1a method gave the best results in terms of RMS, AUE, and maximum error (with regard to *absolute* SFEs). For *relative* SFEs, GVB/6-31G** and MP2/6-31 + G** (CHELPG) charge sets gave the best of all GB/SA results in terms of R , RMS, AUE, and pred r^2 . MC/FEP results (obtained in explicit TIP4P water) were better in terms of R , RMS, and AUE, but with respect to pred r^2 the GVB and MP2 results (obtained in GB/SA water) were better. The molecular database used in these comparisons was rather small and additional work on a bigger database is needed to corroborate these observations. Figure 2c shows the scatter of experimental SFEs and those calculated using the GVB/6-31G** charge sets.

Results from Standard MacroModel Force Fields and Charge Sets

Table Id summarizes the results (based on *absolute* SFEs) obtained with charges from the standard MacroModel force fields (MM2*, MM3*, MMFF, AMBER*, and OPLSA*). Among these, charges assigned by MM2* and MM3* force fields gave the worst performance in reproducing the experimental SFEs. MM3* results were slightly better than MM2* results. MM2* and MM3* charges were derived to fit known functional group dipole moments and do not reflect the distribution of atomic partial charge required by any charge-dependent solvation model. Hence, the default charge sets of MacroModel 5.5²⁷ assigned in conjunction with MM2* and MM3* force fields are not suitable for deriving SFEs. The charge sets assigned by the MMFF force field^{20–24} gave better results. Some improvements in MMFF results were obtained by

optimizing the atomic radii used in the GB (generalized Born) part of the solvation calculation.⁴³ Probably, such improvements could be obtained for any force field results, by rederiving the Born radii specific to each force field. These considerations are beyond the scope of the present work. The default AMBER* charges showed good performance relative to MM2*, MM3*, or MMFF. However, “standard” charge sets of AMBER* were developed for protein and nucleic acid fragments and a small number of organic functionalities, but the user is expected to derive charge sets for other types of organic molecules from high quality *ab initio* calculations. The default OPLSA* charge sets showed the best performance in this series: $R = 0.90$, RMS = 1.06, AUE = 1.02, and pred $r^2 = 0.83$.

Statistical results based on *relative* SFEs are shown in Table IId. Results are better for *relative* SFEs compared with those of *absolute* SFEs (Table Id) for all cases, except the MM2* force field charge sets. The default OPLSA* charge sets gave the best results in this series for *relative* SFEs as well. The original GB/SA parameterization was based on structures optimized using the OPLSA* force field and charge sets; this may be partly responsible for better performance of OPLSA*. The standard OPLSA* charge sets were based on liquid phase simulations in explicit solvent.²⁵ The present GB/SA calculations indicate that results of similar quality can be obtained without the need for explicit solvent simulations. Figure 2d shows the scatter of SFEs determined experimentally and calculated using OPLSA*–GB/SA force field.

SOLVATION FREE ENERGIES FROM ENERGY MINIMIZATION AND TCP CALCULATIONS USING THE GB/SA MODEL

Results from Energy Minimization Calculations

Fifteen pairs of related molecules (shown in Table III) were selected for the calculation of *relative* solvation free energies (ASFEs) using two different protocols and charge sets. For the first protocol, each molecule in each pair was optimized to low gradients using the PRCG method available in MacroModel.²⁷ Two force fields (AMBER*–GB/SA and OPLSA*–GB/SA), which gave better results for the first set of molecules, were evaluated. The *relative* SFEs for the 15 pairs (given by the differences between solvation components of the calculated energies for each pair of molecules) are listed in Table III (columns 3, 4, 5, and 6) along with the corresponding experimental ASFE (column 7). Two

TABLE III.
Solvation Free Energy Differences (in Kilocalories per Mole) for the Pairs Shown in the First Two Columns (beg. and end) Calculated from Minimization Results (Using GB / SA-OPLSA* and AMBER* for Force Fields).

Molecule (beg.)	Molecule (end)	AMBER* GVB	OPLSA* GVB	AMBER* HF	OPLSA* HF	Expt*
Acetone	Acetaldehyde	0.09	0.08	0.35	0.34	0.30
Ethanol	Ethane	5.75	5.81	6.64	6.72	6.80
Ethane	Methanol	-8.23	-8.26	-7.24	-7.31	-6.90
Cyclopentane	Pyrrolidine	-3.97	-4.68	-4.42	-4.69	-6.68
Acetone	Acetic acid	-3.07	-3.01	-2.74	-2.81	-2.90
Benzaldehyde	Benzene	3.17	3.19	5.33	5.33	3.16
Cyclohexane	Piperidine	-2.80	-2.85	-2.87	-2.85	-6.34
Aniline	Benzene	3.93	3.93	3.80	3.81	4.01
Benzene	Pyridine	-0.94	-0.96	-2.60	-2.56	-3.83
Meta-hydroxybenzaldehyde	Benzaldehyde	4.86	4.85	5.17	5.18	4.79
Phenol	Benzene	5.21	5.21	5.89	5.89	5.50
Para-hydroxybenzaldehyde	Benzaldehyde	4.72	4.73	6.12	6.15	6.50
Phenol	Thiophenol	3.95	3.94	5.49	5.47	5.20
1,1,2-Trichloro ethane	Ethane	4.69	4.67	5.15	5.15	3.80
1,1,1-Trichloro ethane	Ethane	2.03	2.00	1.74	1.72	2.10

different charge sets (HF/6-31G* [CHELPG] and GVB/6-31G**) were used in conjunction with the OPLSA*-GB/SA and AMBER*-GB/SA force fields. Because the use of GVB/6-31G** charge sets^{31,32} in conjunction with the OPLSA* force field gave the best results (in terms of *r* and pred *r*²) for the first set, this charge determination procedure was included for comparison with the more widely used HF/6-31G* (CHELPG) procedure. A

statistical summary of the performance of this minimization protocol is given in Table IVa. Results shown in Tables III and IVa clearly indicate that *relative* solvation free energies for pairs of related organic molecules may be estimated with reasonable accuracy from the energy minimization protocol. A high correlation of 0.95 or greater was obtained in all cases and better results were obtained with the use of HF/6-31G* (CHELPG)

TABLE IV.
Sensitivity of Calculated ΔSFEs (Using the GB / SA Model) on Two Protocols: (a) Minimization and (b) TCP Calculations.^a

Protocol	Charge set	Force Field	<i>R</i>	RMS	AUE	Min E	Max E
(a)	GVB / 6-31G**	AMBER*	0.95	1.55	1.09	0.01	3.54
	GVB / 6-31G**	OPLSA*	0.96	1.48	1.03	0.06	3.40
	HF / 6-31G* (CHELPG)	AMBER*	0.97	1.17	0.88	0.05	3.47
	HF / 6-31G* (CHELPG)	OPLSA*	0.97	1.16	0.86	0.04	3.49
(b)	GVB / 6-31G**	AMBER*	0.96	1.51	1.16	0.09	3.01
	GVB / 6-31G**	OPLSA*	0.95	1.51	1.19	0.18	3.02
	HF / 6-31G* (CHELPG)	AMBER*	0.96	1.31	1.01	0.05	3.11
	HF / 6-31G* (CHELPG)	OPLSA*	0.97	1.28	1.00	0.15	3.07

^aCorrelation coefficient (*R*), RMS residual (RMS), average unsigned error (AUE), minimum error (Min E), maximum error (Max E) are shown for each combination of protocol, charge set, and force field.

charge sets, with nearly identical results for OPLSA* and AMBER* force fields: $R = 0.97$, $RMS = 1.2$, and AUE of 0.69. The graph of experimental and calculated $\Delta SFEs$ (using OPLSA*–GB/SA) is shown in Figure 3.

The SFE calculations described here using the GB/SA model consumed very little computer time (of the order of a few seconds of CPU time on an IBM 590/6000 computer for each molecule) and hence SFE calculations using the GB/SA model were computationally more efficient than calculations using MC/FEP protocols⁷ and the explicit solvent models. A comparison of the statistical results of *absolute* and *relative* SFEs for the second set of molecules also shows that estimates of *rela-*

tive SFEs for pairs of related molecules are more accurate than estimates of absolute values.

Solvation Free Energies from Thermodynamic Cycle Perturbation (TCP) Calculations

In principle, it is possible, via TCP methodology, to calculate *absolute* SFEs of organic molecules by causing the solute to disappear in water.⁷ In practice, however, such calculations are successful only for small molecules with about ten heavy atoms (or less), due to the endpoint catastrophe. To test whether the GB/SA water model has advantages over explicit water in these calculations, *absolute* SFEs of four small solutes (water, methane, methanol, ethane) were calculated using the TCP method. As each solute atom converts to a "dummy" atom, the bonds involving dummy atoms also shrink to a preset value. Table V shows the results of these TCP calculations using the GB/SA model for four different dummy bond lengths, 0.25 Å, 0.50 Å, 0.75 Å, and 1.00 Å, along with energy minimization and experimental results. The reported TCP results are well-converged. It is expected that the generalized Born part of the GB/SA solvation energy depends strongly on charges and, when TCP simulations are performed, the assigned dummy bond lengths also play a role in the calculated SFEs. Results shown in Table V demonstrate that TCP-calculated SFEs are sensitive to dummy bond lengths, particularly for molecules with significant partial charges. Notably, the calculated SFE of ethane is insensitive to the dummy bond length because of its negligible partial charge distribution. In the cases of methane, methanol, and water, TCP-calculated SFEs are sensitive to dummy bond lengths due to their significant partial charge distribution. Contrary to the present results, TCP-

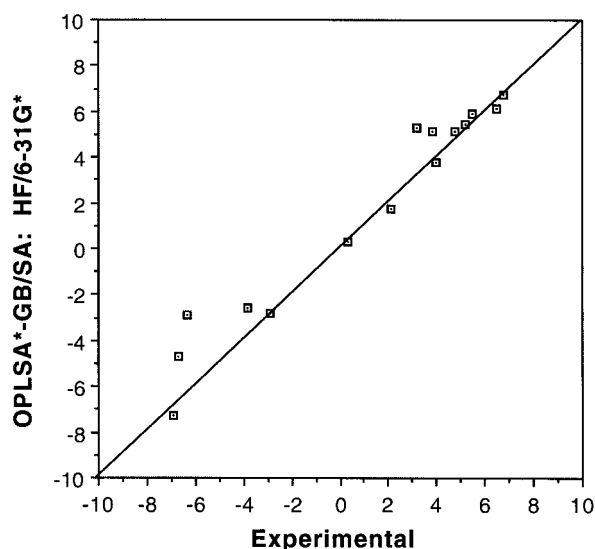


FIGURE 3. Plot of GB / SA calculated (using minimization protocol) vs. experimental *relative* solvation free energies (DSFEs) for the 15 pairs of molecules listed in Table III with HF / 6-31G* (CHELPG) charges using the OPLSA* force field.

TABLE V. Dependence of Calculated SFEs (Using the GB / SA Model and TCP Simulations) on Dummy Bond Lengths in the Cases of Methane, Ethane, Methanol, and Water.^a

Protocol	Du—Du length (Å)	SFE (kcal / mol)			
		Methane	Ethane	Methanol	Water (TIP3P)
TCP	1.00	0.97	2.09	−5.51	−8.50
	0.75	1.09	2.08	−4.28	−6.78
	0.50	1.18	2.08	−3.18	−5.30
	0.25	1.22	2.07	−2.28	−4.12
EM	—	0.93	1.69	−6.11	−8.41
Expt.	—	1.95	1.80	−5.10	−6.30

^a Results using the energy minimization (EM) protocol and corresponding experimental (Expt.) results are also shown.

calculated SFEs for the same molecules using the AMBER force field and explicit SPC/E water gave better agreement and improved convergence, when the dummy bond lengths were reduced.⁴⁴

From the foregoing analysis, it is clear that shrinking bonds through TCP simulations using the GB/SA model (in MacroModel 5.5) leads to spurious results, and the effect is larger in the case of polar molecules. It is, therefore, necessary to set the dummy bond lengths close to (or equal to) the corresponding natural bond lengths for TCP simulations. Table VI shows the *relative* SFEs obtained using the protocol based on TCP calculations for the mutations considered here. In these calculations, a dummy bond length of 1.0 Å was used, due to the reasons discussed earlier. A statistical summary of the results obtained from the TCP calculations is given Table IVb. Data shown in Table IVb and Table VI parallel those shown in Table IVa and Table III. Tables IVb and VI show that TCP calculations provide estimates of solvation free energy differences with reasonable accuracy for the mutations examined. Table VI shows that results obtained in calculations using both AMBER*-GB/SA and OPLSA*-GB/SA force fields are in excellent agreement with experimental results when HF/6-31G* (CHELPG) charge

sets are used. Furthermore, these results are slightly better than those obtained using GVB/6-31G** charge sets for both minimization and TCP protocols. Good agreement with experimental results have been obtained in several TCP applications where HF/6-31G* (CHELPG) charge sets were implemented in conjunction with the AMBER force field and explicit solvent.^{45,46} The graph of experimental and TCP-calculated ASFES (using HF/6-31G* [CHELPG] charge sets and OPLSA*-GB/SA force field) is shown in Figure 4. Overall, the results are of comparable accuracy to those obtained by energy minimization calculations alone. With respect to maximum error (max E), TCP results appear to be better, but with respect to other statistical parameters, both TCP and energy minimization results are equivalent. Therefore, there is no significant advantage of computationally expensive TCP calculations over simple energy minimizations in the determination of SFEs for small solutes using the GB/SA solvent model. However, whereas FEP gives stable results, energy minimization requires averaging over several minima with the use of explicit solvent.¹⁵ In principle, TCP calculations are more appropriate for conformationally flexible solutes, although, in practice, efficient interconversion of conformers is hard to

TABLE VI.
Solvation Free Energy Differences (in Kilocalories per Mole) for Pairs Shown in First Two Columns (beg. and end) as Calculated from TCP Simulations (Using GB / SA-OPLSA* and AMBER* Force Fields) Using GVB / 6-31G (GVB) and HF / 6-31G*-CHELPG (HF) Charge Sets.**

Molecule (beg.)	Molecule (end)	AMBER* GVB	OPLSA* GVB	AMBER* HF	OPLSA* HF	Expt*
Acetone	Acetaldehyde	-0.17 ± 0.08	-0.20 ± 0.10	0.07 ± 0.08	0.04 ± 0.09	0.30
Ethanol	Ethane	5.37 ± 0.08	5.42 ± 0.07	6.13 ± 0.10	6.30 ± 0.09	6.80
Ethane	Methanol	-8.67 ± 0.07	-8.76 ± 0.06	-7.68 ± 0.07	-7.78 ± 0.06	-6.90
Cyclopentane	Pyrrolidine	-4.27 ± 0.06	-4.46 ± 0.11	-4.21 ± 0.06	-4.57 ± 0.11	-6.68
Acetone	Acetic acid	-3.45 ± 0.60	-3.70 ± 0.57	-3.26 ± 0.55	-3.24 ± 0.65	-2.90
Benzaldehyde	Benzene	2.29 ± 0.12	2.33 ± 0.07	4.24 ± 0.10	4.22 ± 0.15	3.16
Cyclohexane	Piperidine	-3.33 ± 0.12	-3.32 ± 0.05	-3.23 ± 0.06	-3.27 ± 0.04	-6.34
Aniline	Benzene	3.92 ± 0.13	3.83 ± 0.08	3.70 ± 0.13	3.67 ± 0.15	4.01
Benzene	Pyridine	-1.16 ± 0.04	1.15 ± 0.03	-2.80 ± 0.04	-2.76 ± 0.03	-3.83
Meta-hydroxy-benzaldehyde	Benzaldehyde	5.23 ± 0.21	5.16 ± 0.22	5.72 ± 0.26	5.58 ± 0.24	4.79
Phenol	Benzene	4.92 ± 0.08	4.92 ± 0.10	5.65 ± 0.09	5.65 ± 0.10	5.50
Para-hydroxy-benzaldehyde	Benzaldehyde	5.12 ± 0.16	5.13 ± 0.17	5.99 ± 0.09	6.00 ± 0.09	6.50
Phenol	Thiophenol	5.87 ± 0.03	5.86 ± 0.08	7.62 ± 0.06	7.61 ± 0.05	5.20
1,1,2-Trichloroethane	Ethane	3.58 ± 0.08	3.21 ± 0.09	3.85 ± 0.07	3.44 ± 0.10	3.80
1,1,1-Trichloroethane	Ethane	1.30 ± 0.03	1.26 ± 0.04	1.00 ± 0.04	0.97 ± 0.03	2.10

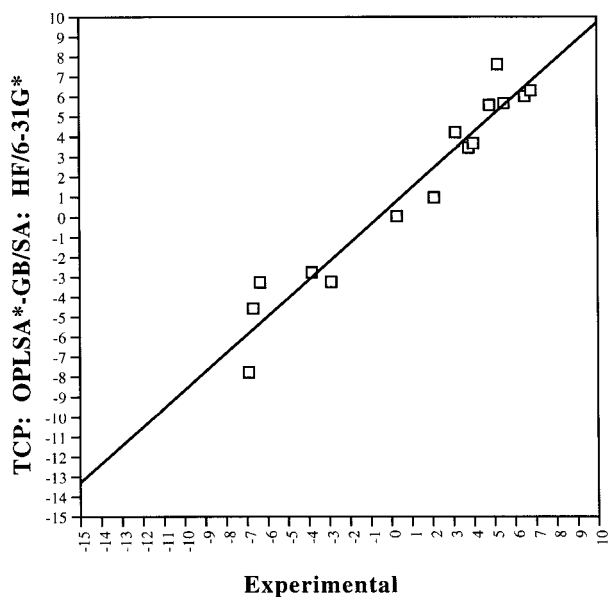


FIGURE 4. Plot of GB / SA calculated (using TCP protocol) vs. experimental *relative* solvation free energies (DSFEs) for the 15 pairs of molecules listed in Table VI with HF / 6-31G* charges using the OPLSA* force field.

achieve in most simulation protocols. Because TCP calculations using the implicit solvent are computationally much faster than corresponding explicit solvent calculations, the TCP approach using the GB/SA model holds considerable promise in the treatment of larger complexes such as host–guest systems⁴⁷ and protein–ligand complexes.

All of the aforementioned results were based on a fast analytical approach to Born radii used in the GB/SA model.⁴⁸ A good agreement between calculated and experimental SFEs suggests an appropriate representation of Born radii in the GB/SA model. Parameters associated with this approach have recently been optimized to reproduce Poisson–Boltzmann G_{pol} energies for 189 organic and biological molecules.⁴⁸ SFEs computed using both numerical and analytical approaches yielded similar results, although, in some cases, slightly better results were obtained with numerically calculated Born radii.

Conclusion

The present results clearly show that the GB/SA solvent model is an effective tool for estimating solvation free energies of small organic molecules. This model gave reasonably accurate estimates of *absolute* SFEs for small organic molecules when

geometries and electrostatic-potential-derived (CHELPG) charge sets from high-level *ab initio* (Gaussian-92) calculations or GVB/6-31G** charge sets were used. Among charge sets obtained from semiempirical MO methods, “class IV” charge sets from AM1/CM1a calculations gave the best results. Of all the standard force fields implemented in MacroModel, the OPLSA* force field gave the best results for the molecules considered here. However, at least in part, the best results with the use of OPLSA* force field may be attributed to the fact that the GB/SA solvent model was parameterized with the OPLSA force field. SFE results with HF/6-31G* (CHELPG) charge sets were much better than those with default or Mulliken charge sets, and inclusion of correlation effects via MP2 or GVB calculations improved SFE estimates further. Overall, the GB/SA results were similar in quality and accuracy to the results of MC/FEP calculations using the explicit TIP4P water model. Importantly, GB/SA calculations have the advantage of simplicity and computational efficiency and, therefore, they can be used for rapid estimation of solvation free energies for large databases of small organic molecules.

It was shown further that, in most cases, *relative* SFEs can be estimated more accurately than absolute SFEs, owing to error-cancellation effects. Two different protocols, based on energy minimization and TCP methodology, were applied and tested. A comparison of these results indicated that *relative* SFEs obtained from energy minimization calculations were similar in accuracy to the more sophisticated TCP simulations, although TCP simulations were more accurate for flexible molecules. However, SFEs determined using the TCP method and the GB/SA model were sensitive to dummy bond lengths, particularly for polar solutes. In such cases, the dummy bond lengths should be set closer to “natural” bond lengths to avoid spurious results.

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